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CLINICAL THERAPEUTICS

Safety and Efficacy of Prolonged Use of Dalbavancin in Bone and Joint Infections

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ABSTRACT Dalbavancin is a lipoglycopeptide with potent activity against Gram-positive microorganisms, a long half-life, a favorable safety profile, and a high concentration in bone, which makes it an interesting alternative for treatment of osteoarticular infections. We performed a multicentric retrospective study of all patients with an osteoarticular infection (septic arthritis, spondylodiscitis, osteomyelitis, or orthopedic implant-related infection) treated with at least one dose of dalbavancin be-

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tween 2016 and 2017 in 30 institutions in Spain. In order to evaluate the response, patients with or without an orthopedic implant were separated. A total of 64 patients were included. *Staphylococcus epidermidis* and *Staphylococcus aureus* were the most frequent microorganisms. The reasons for switching to dalbavancin were simplification (53.1%), adverse events (25%), or failure (21.9%). There were 7 adverse events, and no patient had to discontinue dalbavancin. In 45 cases, infection was related to an orthopedic implant. The implant material was retained in 23 cases, including that in 15 (65.2%) patients that were classified as cured and 8 (34.8%) that presented improvement. In 21 cases, the implants were removed, including those in 16 (76.2%) cases that were considered successes, 4 (19%) cases were considered improved, and 1 (4.8%) case that was considered a failure. Among the 19 cases without implants, 14 (73.7%) were considered cured, 3 (15.8%) were considered improved, and 2 (10.5%) were considered failures. The results show that dalbavancin is a well-tolerated antibiotic, even when >2 doses are administered, and is associated with a high cure rate. These are preliminary data with a short follow-up; therefore, it is necessary to gain more experience and, in the future, to establish the most appropriate dose and frequency.

KEYWORDS bone and joint infections, dalbavancin, osteomyelitis, prosthetic joint infection

Adult bone and joint infections, including osteomyelitis, septic arthritis, and orthopedic implant-related infections, are common and require prolonged antibiotic treatment to eradicate planktonic, biofilm, intracellular, and intracanaliculus bacteria that are frequently involved in these infections (1–3). Although the current guidelines for native vertebral osteomyelitis and prosthetic joint infections (PJI) recommend at least 6 weeks of intravenous treatment, antimicrobial therapy with high oral bioavailability is an alternative to intravenous administration (4–6). Good outcomes have been reported with the oral combination of a fluoroquinolone and rifampin (7–10), particularly for implant-associated infections. However, other oral alternatives combined with rifampin have been associated with lower remission rates (8, 11).

In addition, a recent article measuring the postdischarge adherence to oral antibiotics by an electronic bottle cap that recorded each pill bottle opening demonstrated a significant difference between self-reported adherence and electronically measured adherence (57% versus 96%; $P < 0.0001$) (12). In this study, poor adherence was associated with a lower clinical response at 30 days. It is reasonable to expect an even lower adherence rate when the antibiotic duration is longer than 2 weeks. Therefore, other alternatives for bone and joint infections are necessary, most especially for those caused by fluoroquinolone-resistant staphylococci (13) and for patients at risk of low adherence to oral treatment (e.g., older people, homeless people, drug addicts).

The aim of the present study was to review the clinical characteristics, outcome, and adverse events observed in patients with bone and joint infections treated with at least one dose of dalbavancin, a long-acting lipoglycopeptide, since it was approved in Spain.

RESULTS

A total of 64 patients were included in the study. The mean age was 63 (standard deviation [SD], 15.7) years, and 39 (60.9%) were male. The most common comorbidities were diabetes mellitus in 14 cases (21.9%), chronic obstructive pulmonary diseases (COPD) in 7 cases (10.9%), cardiac disease in 7 cases (10.9%), chronic renal failure in 6 cases (9.4%), malignant tumor in 6 cases (9.4%), and rheumatoid arthritis in 5 (7.8%). The most common microorganisms were *Staphylococcus epidermidis* ($n = 30$, 46.9%) and *Staphylococcus aureus* ($n = 14$, 21.9%), which were methicillin resistant in 93.3% (28 out of 30) and 64.3% (9 out of 14) of the cases, respectively (Table 1). All enterococci were susceptible to vancomycin. Five (11.1%) patients had a polymicrobial infection, and in two of them a Gram-negative organism was also isolated. The reasons for

TABLE 1 Etiology according to type of infection

Microorganism(s)	No. (%) of patients with:	
	Implant-associated infection ($n = 45$)	Bone or joint infection ($n = 19$)
Staphylococcus epidermidis	26 (57.7)	4 (21)
Staphylococcus aureus	4 (8.9)	10 (52.6)
Staphylococcus lugdunensis	2 (4.4)	0
Staphylococcus capitis	1 (2.2)	0
Streptococcus pneumoniae	1 (2.2)	0
Enterococcus faecalis	4 (8.9)	1 (5.2)
Enterococcus faecium	3 (6.6)	1 (5.2)
Corynebacterium striatum	2 (4.4)	1 (5.2)
Streptococcus spp.[a]	0	3 (15.7)
Anaerobes[b]	2 (4.4)	1 (5.2)
Gram negatives[c]	2 (4.4)	0
Polymicrobial	5 (11.1)	3 (15.7)
Negative culture	3 (6.6)	1 (5.2)

[a]*Streptococcus* spp. included one *S. agalactiae*, one *S. pyogenes*, and one *S. sanguinis*.
[b]Anaerobes included one *Clostridium celerecrescens* and two *Propionibacterium acnes*.
[c]Gram negatives included one *Escherichia coli* and one *Pseudomonas aeruginosa* (both were isolated with a Gram-positive microorganism).

switching to dalbavancin were simplification of the regimen ($n = 34$, 53.1%), adverse events related to the previous antibiotic ($n = 16$, 25%), or failure during treatment with the previous antibiotic ($n = 14$, 21.9%). The first dose was 1,000 mg in 50 cases, 1,500 mg in 12, and 500 mg and 750 mg in 1 case each. In 9 cases, a single dose was administered, in 54 cases, dalbavancin was administered once weekly (500 mg) for a median (interquartile range [IQR]) of 5 (3 to 7) doses, and in 1 case, 4 doses of 1,500 mg were administered biweekly. There were 7 adverse events: 3 gastrointestinal problems, 1 self-limited rash, 1 phlebitis, 1 self-reported asthenia, and 1 case with a documented increase of 0.5 mg/dl of serum creatinine. In none of the cases did treatment with dalbavancin have to be stopped due to the adverse events.

The characteristics and outcomes of patients grouped as cases with implant-associated infections ($n = 26$ prosthetic joint infections; $n = 19$ other-implant infections) and bone or joint infections ($n = 19$) are depicted in Tables 2 and 3.

Among the 45 cases with an orthopedic implant infection, the outcomes were evaluated in 44 cases because one patient was lost during follow-up. In 52.3% ($n = 23$) of the cases, the implant was retained. Of these, 15 cases (65.2%) were classified as successes and 8 cases (34.8%) were classified as improvements. In 47.7% ($n = 21$), the implant was removed and 16 (76.2%) were classified as successes, 4 (19%) were classified as improvements, and 1 (4.8%) was classified as a failure after a median (IQR) follow-up of 157 (75.5 to 273.5) days after the last dalbavancin dose. Among the 19 cases with a bone or joint infection and after a median (IQR) follow-up of 164 (93 to 262.5) days after the last dalbavancin dose, 14 (73.7%) were classified as successes, 3 (15.8%) were classified as improvements, and 2 (10.5%) were classified as failures. In one failure, the infection persisted and the patient died 5 months after finishing dalbavancin for an unrelated event, and the other failure was a patient with sacral osteomyelitis due to methicillin-resistant *S. aureus* who had received a single dose of dalbavancin to simplify the antibiotic treatment and had relapsed after 1 month. The outcomes of patients according to the type of infection, the reason for starting dalbavancin, the type of microorganism, and the concomitant use of rifampin are summarized in Fig. 1.

DISCUSSION

Dalbavancin is a new semisynthetic lipoglycopeptide approved in the United States and Europe for acute bacterial skin and skin and soft tissue infections with potent activity against staphylococci, including methicillin-resistant, heterogeneous vancomycin-intermediate *S. aureus* (hVISA), and VISA strains and vancomycin-susceptible enterococci ($MIC_{90} \leq 0.12$ mg/liter) (14, 15). The main advantage of this antibiotic is its long

TABLE 2 Characteristics and outcomes of patients with implant-associated infections ($n = 45$)

Variable[f]	Value
Age (yrs), mean (SD)	64 (15)
Male sex, no. (%)	24 (53.3)
Comorbidity, no. (%)	
Diabetes mellitus	7 (15.5)
Rheumatoid arthritis	3 (6.6)
Chronic renal failure	5 (11.1)
Cancer	5 (11.1)
COPD	4 (8.8)
Liver cirrhosis	2 (4.4)
Cardiac disease	3 (6.6)
Type of implant, no. (%)	
Joint prosthesis	26 (57.8)
Hip	13
Knee	10
Shoulder	3
Other implant	19 (42.2)
Spine	11
Long bone	5
Other	3
Median (IQR) no. of days from implantation to infection diagnosis	115 (27–424)
Fever, no. (%)	13 (28.8)
Local signs of infection at admission, no. (%)	31 (68.8)
Wound drainage, no. (%)	21 +(46.6)
Fistula, no. (%)	11 (24.4)
Median (IQR) leukocyte count (cells/mm^3)	7,300 (5,750–9,925)
Median (IQR) SCr (mg/dl) before dalbavancin treatment[a]	1 (0.6–1)
Median (IQR) highest SCr (mg/dl) during dalbavancin[a]	1 (0.6–1)
Baseline CRP (mg/dl)[b]	5 (2.7–11.7)
Last control CRP (mg/dl)[c]	1 (0.3–1.3)
Median (IQR) no. of days of antibiotics prior to dalbavancin treatment	41 (21–87)
Reason for starting dalbavancin, no. (%)	
Failure to prior antibiotic	12 (26.6)
Simplification	23 (51.1)
Toxicity to prior antibiotic	10 (22.2)
Median (IQR) no. of dalbavancin doses	5 (3–8)
Other concomitant antibiotic, no. (%)	
Rifampin	8 (17.7)
Other	7 (15.5)
Outcome, no. (%)[d]	
Implant retention	23 (52.3)
Success	15
Improvement	8
Failure	0
Implant removal	21 (47.7)
Success	16
Improvement	4
Failure	1
Death, no. (%)[e]	1 (2.2)
Median (IQR) no. of days of follow-up	157 (75.5–273.5)

[a]Measured in 36 patients.
[b]Measured in 42 patients.
[c]Measured in 41 patients.
[d]Evaluation from 44 cases. One case was lost during follow-up.
[e]Not related to the infection.
[f]COPD, chronic obstructive pulmonary disease; SCr, serum creatinine; CRP, C-reactive protein. No. (%), number (percent) of patients.

TABLE 3 Characteristics and outcomes of patients with bone or joint infections

Variable[d]	Value
Age (yrs), mean (SD)	61 (17.5)
Male sex, no. (%)	15 (78.9)
Comorbidity, no. (%)	
Diabetes mellitus	7 (36.8)
Rheumatoid arthritis	2 (10.5)
Chronic renal failure	1 (5.2)
Cancer	1 (5.2)
COPD	3 (15.7)
Liver cirrhosis	0
Cardiac disease	4 (21)
Type of bone or joint infection (%)	
Osteomyelitis	12 (63.1)
Septic arthritis or spondylodiscitis	7 (36.9)
Fever, no. (%)	3 (15.7)
Local signs of infection at admission, no. (%)	11 (57.9)
Wound drainage, no. (%)	5 (26.3)
Fistula, no. (%)	3 (15.7)
Median (IQR) leukocyte count (cells/mm^3)	9,545 (8,235–14,085)
Median (IQR) SCr (mg/dl) before dalbavancin treatment[a]	1 (0.6–1)
Median (IQR) highest SCr (mg/dl) during dalbavancin treatment[a]	1 (0.7–1.2)
Baseline CRP (mg/dl)	14 (4.4–13.7)
Last control CRP (mg/dl)[b]	1 (0.2–1.3)
Median (IQR) no. of days of antibiotics prior to dalbavancin treatment	32 (21–46)
Reason for starting dalbavancin, no. (%)	
Failure to prior antibiotic	2 (10.5)
Simplification	11 (57.9)
Toxicity to prior antibiotic	6 (31.5)
Median (IQR) no. of dalbavancin doses	2 (2–4)
Other concomitant antibiotic, no. (%)	
Rifampin	0
Other	6 (31.5)
Outcome, no. (%)	
Success	14 (73.6)
Improvement	3 (15.7)
Failure	2 (10.5)
Death, no. (%)[c]	3 (15.7)
Median (IQR) no. of days in follow-up	164 (93–262.5)

[a]Measured in 17 patients.
[b]Measured in 18 patients.
[c]Not related to the infection.
[d]COPD, chronic obstructive pulmonary disease; SCr, serum creatinine; CRP, C-reactive protein. No. (%), number (percent) of patients.

half-life (180 to 240 h), which allows a once weekly or biweekly intravenous administration, reducing the use of vascular catheters and saving hospital stays (16). Bone and joint infections, particularly when the implant is not removed, require at least 6 to 12 weeks of antibiotic treatment according to the majority of current guidelines. A recent unblinded and randomized trial (OVIVA) confirmed that oral antibiotic treatment is as effective as intravenous administration in bone, joint, or metalware-associated infections (17). The better results with oral antibiotics have been demonstrated with levofloxacin plus rifampin; however, other oral alternatives combined with rifampin have been associated with lower remission rates (8, 11), in part due to a worse safety profile but also to a reduction in the serum concentration of companion drugs like clindamycin, co-trimoxazole, linezolid, or fusidic acid (18–21), in contrast to what has been shown with fluoroquinolones (10). Therefore, more alternatives are needed for the

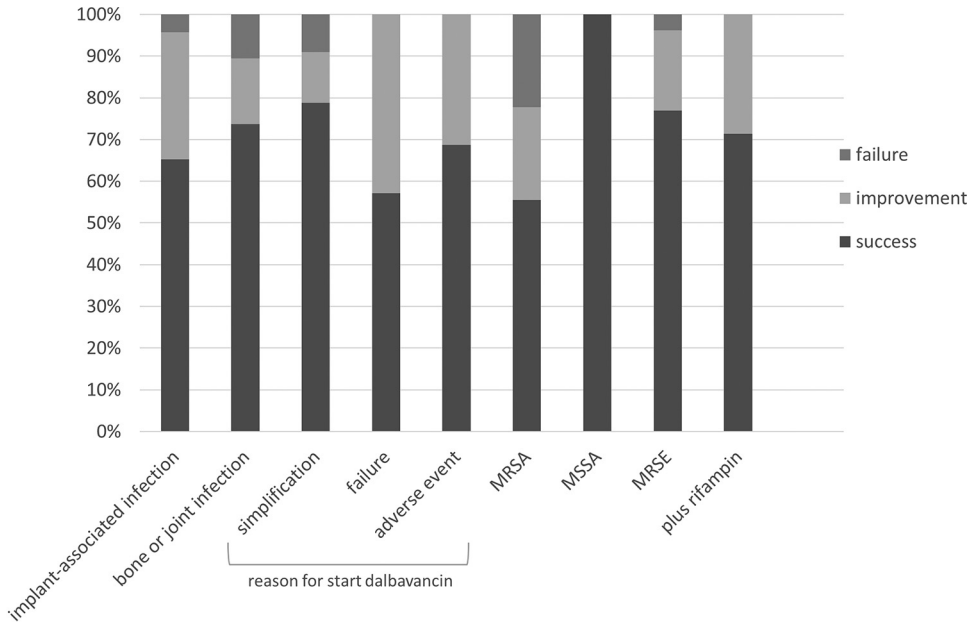

FIG 1 Outcome of patients according to the type of infection, the reason for starting dalbavancin, etiology, and concomitant use of rifampin.

treatment of bone and joint infections (22). The first conclusion of our study is that dalbavancin is well tolerated, with minor adverse events without any treatment interruption or evidence of nephrotoxicity. Indeed, dalbavancin is a derivative of teicoplanin, and it is significantly less toxic than vancomycin (23). In line with this, dalbavancin was infused over 30 min, and in only one case, a skin rash was reported after the first dose but did not recur after the subsequent ones. This makes dalbavancin an attractive drug for infusion at home by OPAT (outpatient parenteral antibiotic treatment) systems. About 50% of the cases received dalbavancin once the infection was controlled in order to complete antibiotic treatment, and the success rate was almost 80%. These results support a recent report showing a >90% success rate with dalbavancin as a sequential treatment for infective endocarditis caused by Gram-positive cocci (24). On the other hand, the success rate among patients that received dalbavancin after failure with a prior antibiotic was >50%, suggesting a role for dalbavancin as a salvage therapy in some cases. The efficacy of dalbavancin in these infections could be partly attributed to its efficacy against biofilms (25, 26) and its bone diffusion. Dunne et al. (27) determined the concentrations in synovial fluid and bone after 14 days of 1,000 mg of dalbavancin to be 14 mg/liter and 4 μg/g, respectively, both above the MIC_{90} of dalbavancin for staphylococci and enterococci. This result suggests that a biweekly regimen is possible and even more convenient. Finally, although the number of patients that received rifampin concomitantly with dalbavancin was low, the success rate was 70%, suggesting that this combination is not subjected to pharmacokinetic interactions and might be a valid alternative to the regimen of levofloxacin plus rifampin for orthopedic implant infections. These results are in agreement with a not-yet-published randomized, open-label trial comparing dalbavancin at 1,500 mg on days 1 and 8 versus the standard of care (SOC) for osteomyelitis (excluding implant infections). The researchers showed a clinical cure rate of 94% versus 88% after 1 year of follow-up, and the drug was well tolerated (U. Rappo, V. Shevchenko, O. Shevchenko, A. Jandourek, P. Gonzalez, S. Puttagunta, M. Dunne, A. Suen, V. MasCasullo, D. Melnick, R. Miceli, M. Kovacevic, and G. De Bock, presented at the 28th European Congress of Clinical Microbiology and Infectious Diseases [ECCMID], 21 to 24 April 2018).

Our study has some limitations. The first limitation is the retrospective nature of the study as well as the heterogeneity of the patients. Second, the majority of treatments

began after the infection was under control, which could lead to overestimation of the success rate, and the follow-up period, which in general should be 2 years for these infections, was short.

In conclusion, ≥2 doses of dalbavancin is a safe regimen for treating bone and joint infections, and our results show an acceptable success rate that should be confirmed in future prospective studies.

MATERIALS AND METHODS

Study design. This was an observational and retrospective study in which participant centers were invited to include all patients with a bone or joint infection who had been treated with at least one dose of dalbavancin from March 2016 to November 2017.

The clinical medical records were retrospectively reviewed, and the following variables were collected: age, sex, comorbidities (diabetes mellitus, rheumatoid arthritis, chronic obstructive pulmonary disease, liver cirrhosis, cardiovascular disease, and neoplasia), type of infection (septic arthritis, osteomyelitis, or orthopedic implant-related infection), location of the infection, clinical manifestations (fever, inflammatory signs, ulcer, wound drainage, or fistula), radiology performed for the diagnosis (computer tomography, magnetic resonance, scintigraphy), laboratory tests (leukocyte count, hemoglobin, platelet count, baseline and highest serum creatinine level during dalbavancin treatment, C-reactive protein, erythrosedimentation rate), microbiology data (sample, type of microorganism, and susceptibility pattern), surgical treatment (debridement, implant removal), antibiotic treatment prior to dalbavancin administration, initial dalbavancin and maintenance dose, frequency and number of doses, and potentially related adverse events. Each physician decided the dose and frequency of administration. In cases with a polymicrobial infection, all microorganisms isolated received adequate antibiotic treatment.

Outcome variable definitions. Treatment success was defined as the absence of clinical signs of infection at the latest medical visit, without the need for additional surgeries or antibiotic treatment for the same infection during or after finishing dalbavancin. The infection was considered improved when no evidence of infection was present at the latest medical visit but suppressive antibiotic therapy was initiated after finishing dalbavancin. Failure was defined as persistent or reappearing signs of infection, the need to perform additional surgeries to control the infection after starting dalbavancin, or occurrence of adverse events requiring the discontinuation of dalbavancin treatment or infection-related death.

Ethics. The study was approved by our institutional review board, which waived the requirement of informed consent owing to the design of the study.

Statistical analysis. Variables were gathered in an Excel file, and a descriptive analysis was performed using mean and standard deviation (SD) or median and interquartile range (IQR) as descriptors of the cohort. For the outcome description, patients were divided in two groups, those with an orthopedic implant infection and those with a bone or joint infection, including osteomyelitis, septic arthritis, and spondylodiscitis.

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